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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/607,974	SERRERO, GINETTE	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/6/06 and 6/5/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's Amendment and Remarks filed June 5, 2006.

Claims 28, 31, 35, and 35 have been amended. New claim 38 is acknowledged.

Claims 28-38 are pending in the instant application.

Claims 28-38 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

Applicant's information disclosure statements filed April 6, 2006 and June 5, 200-6 are acknowledged. The submissions are in compliance with the provisions of 37 CFR §1.97. Accordingly, the Examiner has considered the information disclosure statements, and signed copies are enclosed herewith.

Double Patenting

In the previous Office Action mailed February 3, 2006, claims 28-37 were rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 5-7 and 10 of U.S. Patent No. 6,670,183 ('183). **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed February 3, 2006.

Response to Arguments

In response to this rejection, Applicants argue that the claims of the '183 Patent relate to *in vitro* or *ex vivo* administration of a GP88 antisense oligonucleotide, whereas the claims of the present application relate to *in vivo* administration. Applicants contend that for this reason, the present claims are not obvious variations of the claims of the '183 patent.

Applicant's arguments and contentions have been fully considered but are not found persuasive. First, Applicant is reminded that during patent examination, the claims are given the broadest reasonable interpretation consistent with the specification. See MPEP § 2111-2116.01. The instant claims are drawn to a method of inhibiting the growth of a tumor cell, or a method of inhibiting the expression of PC cell derived growth factor protein in a cell, comprising administering a PC cell derived growth factor antisense oligonucleotide to the tumor cell, wherein said antisense oligonucleotide inhibits the growth of the tumor cell or inhibits the expression of PC cell derived growth factor. Given their broadest reasonable interpretation, the instant claims imply *in vitro*, *ex vivo*, or *in vivo* applicability.

Second, it is noted that the instant claims do not recite that the instant methods are performed exclusively *in vivo*. Thus, absent the explicit claim language of "*in vivo*", the claims are interpreted broadly to include *in vitro*, *ex vivo*, or *in vivo* applicability.

Claim Rejections - 35 USC § 112

In the previous Office Action mailed February 3, 2006, claims 28-37 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention since the term "GP88" is not clearly defined. **This rejection is withdrawn** against claims 28-33 and 35-37 in view of Applicant's Amendment filed June 5, 2006. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Amendment to the claims to recite the full name of the growth factor. **However, this rejection is maintained** against claim 34 for the reasons of record set forth in the previous Office Action mailed February 3, 2006.

Response to Arguments

In response to this rejection, Applicants argue that, to further prosecution, the claims have been amended to recite the full name of the growth factor. However, the Examiner would like to point Applicant to claim 34, where the term, "GP88" is recited in line 4. In this light, claim 34 is indefinite because the term "GP88" is not clearly defined. Since abbreviations often have more than one meaning, it is suggested that inserting the full name of the growth factor would overcome the instant rejection.

In the previous Office Action mailed February 3, 2006, claims 28-37 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting the growth of a tumor cell or a method of inhibiting

the protein expression of 88kDa glycoprotein growth factor (GP88) in a cell, comprising the subcutaneous injection of a GP88 antisense oligonucleotide targeted to SEQ ID NO:16, using primer pairs SEQ ID NO:12 and SEQ ID NO:14, wherein said antisense inhibits the growth of the tumor cell or inhibits the protein expression of GP88, does not reasonably provide enablement for a method of inhibiting the growth of a tumor cell or a method of inhibiting the protein expression of GP88 in a cell, comprising any route of administration of any antisense targeted to GP88, wherein said antisense inhibits the growth of the tumor cell or inhibits the protein expression of GP88. **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed February 3, 2006. It is noted that new claim 38 is also included in the instant rejection.

Response to Arguments

In response to this rejection, Applicants argue that the present claims are limited to a PC cell derived growth factor antisense oligonucleotide. Applicants contend that the instant specification provides ample guidance in determining and selecting effective antisense sequences (e.g. size and target regions) to be used in the methods claimed. Applicants also contend that the instant specification teaches that sequences may be screened *in vitro* for potency of their antisense activity by measuring the inhibition of GP88 in cells in culture. Applicants argue that such screening techniques are routine and are not considered undue experimentation.

Applicant's arguments and contentions have been fully considered, but are not found persuasive because, while the claims are limited to a PC cell derived growth

factor antisense oligonucleotide, the claims encompass *in vivo* applicability where the art, at the time of Applicant's filing, has shown that antisense oligonucleotides are only enabled for therapeutic purposes on a case-by-case basis. For example, see the discussions of Agrawal et al. Branch, A.D., and Jen et al. in the previous Office Action mailed February 3, 2006, at pages 7-10. Additionally, based on these discussions, a person skilled in the art would recognize that predicting the efficacy of a compound, particularly an antisense compound, *in vivo,* based solely on its performance *in vitro* is unpredictable. For example, Patil et al. (The AAPS Journal, 2005 Vol. 7, pages E62-E77) discuss, "[T]he resulting random delivery profile of DNA-based drugs is further complicated by a lack of *in vivo/in vitro* correlation of their pharmacological outcomes" (see page E62, first paragraph). Thus, although the specification considers general methodologies of using *any* PC cell derived growth factor antisense oligonucleotide *in vivo*, such a disclosure would not be considered enabling since the state of antisense-mediated gene inhibition is highly unpredictable as detailed in the previous Office action mailed February 3, 2006. See pages 7-10.

Applicants also argue that it is well recognized that antisense oligonucleotides are successfully used for therapeutic purposes. Applicants point the Examiner to Crooke, S.T., (Current Molecular Medicine, 2004, Vol. 4, pages 465-487) and Aboul-Fadl, T., (Current Medicinal Chemistry, 2005 Vol. 12, pages 2193-2214).

This argument has been fully considered, but is not found persuasive. While the Examiner agrees that some antisense oligonucleotides have been successfully used for therapeutic purposes, such successes are not the rule, but few and far between. For

example, a very recent review states, "[D]espite many favorable characteristics and signs of possible clinical victories, the introduction of DNA-based drugs for human use can be best described as limited, with rare successes" (see Patil et al, The AAPS Journal, 2005 Vol. 7, see page E62, first paragraph). Further, it is noted that the instant claims have been afforded priority to May 23, 1997. A person skilled in the art would recognize that as far back as 1997, antisense gene therapy was highly unpredictable. For further explanation, see the discussions of Agrawal et al. Branch, A.D., and Jen et al. in the previous Office Action mailed February 3, 2006, at pages 7-10. Further, the Crooke and Aboul-Fadl references that Applicants point the Examiner to were published many, many years after Applicant's priority date. While the Examiner agrees that, over the years, many advances have been made in the antisense therapy art, more progress needs to be made before antisense oligonucleotides are routinely administered *in vivo* to result in a therapeutic effect. Therefore the references of Branch, A.D.(1998), Jen et al. (2000) and Agrawal et al. (2000), relied upon by the Examiner, and not Crooke, S.T. (2004) or Aboul-Fadl (2005), relied upon by Applicant, better indicate the state of the art of antisense therapy at the time of Applicant's invention.

Applicants also argue that at the time the Application was filed, those of ordinary skill in the art would have appreciated that a wide variety of delivery routes were available for oligonucleotides. Applicants point the Examiner to Wang et al. (Antisense and Nucleic Acid Drug Development, 2003 Vol. 13, pages 169-189) and Brysch et al. (Cellular and Molecular Neurobiology, 1994 Vol. 14, No. 5).

This argument has been fully considered, but is not found persuasive. While the

Examiner agrees that at the time the Application was filed, a wide variety of delivery routes were available for oligonucleotides, only subcutaneous injection of a GP88 antisense targeted to SEQ ID NO:16, using primer pairs SEQ ID NO:12 and SEQ ID NO:14 was demonstrated to carry out the function of the instant claims. Also, regarding the Wang et al. reference (2003), the Examiner acknowledged that Wang et al. state, "[A]n ever expanding body of *in vivo* animal experiments has shown that parenterally delivered phosphorothioate [oligonucleotides] (PS-ODNs) can be effectively absorbed by animals even in simple saline solutions. These data quickly led to the conclusion that delivery is not a problem in the application of [oligonucleotides] *in vivo*". However, Wang et al. also teach, "[M]any groups have reported exciting *in vitro* results aims at improving tumor delivery. Unfortunately, few of these results have been successfully translated into animal models" (see page 179, first paragraph). Therefore, given the discussions of Wang et al., it is clear and evident that delivery of antisense oligonucleotides in a whole animal (*in vivo*) is not predictable.

Applicants argue that the instant specification provides ample guidance for a variety of effective delivery methods. Applicants point the Examiner to the instant specification at paragraphs [0117] – [0119]. Applicants contend that based on this guidance, one of ordinary skill in the art would have been able to practice the invention.

Applicant's arguments and contentions have been fully considered, but are not found persuasive. While the Examiner agrees that at the time the Application was filed, a wide variety of delivery routes were available for oligonucleotides, only subcutaneous injection of a GP88 antisense targeted to SEQ ID NO:16, using primer pairs SEQ ID

NO:12 and SEQ ID NO:14 was demonstrated to carry out the function of the instant claims. In light of the fact that the feasibility of antisense therapy for one antisense does not demonstrate the feasibility of antisense therapy for a wholly different antisense oligonucleotide (see Agrawal et al.), one of ordinary skill in the art would have to perform undue experimentation to practice the invention over the scope claimed. The quantity of undue experimentation would include the determination of what specific cells to target with PC cell derived growth factor antisense oligonucleotides and how to specifically deliver said antisense oligonucleotides to an organism *in vivo* (whole organism) at a concentration effective to result in inhibiting tumor growth of a cell in a whole animal or inhibiting the expression of PC cell derived growth factor protein expression in a cell in a whole animal. Additionally, this undue experimentation would include the determination of such factors as dosage, route of administration, disposition of the antisense oligonucleotide in cells, and the half-life and stability of the oligonucleotide molecule *in vivo*. Given the art recognized unpredictability of the therapeutic application of antisense *in vivo* (whole organism), this determination would not be routine and would require undue trial and error experimentation. Thus, the Wands factors have been reweighed and favor undue experimentation.

After careful reconsideration of the claims, a new ground(s) of rejection is made of record as detailed below:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a written description rejection.**

The subject matter of the instantly claimed invention is drawn to a method of inhibiting the growth of a tumor cell, or a method of inhibiting the expression of PC cell derived growth factor protein in a cell, comprising administering a PC cell derived growth factor antisense oligonucleotide to the tumor cell, wherein said antisense oligonucleotide inhibits the growth of the tumor cell or inhibits the expression of PC cell derived growth factor.

The instant specification discloses the cDNA sequence of mouse GP88/granulin/PC cell derived growth factor (see Figure 8) and the nucleotide sequence of human GP88/granulin/PC cell derived growth factor (GenBank Accession Number M75161) (see Figure 9). The instant specification also teaches that a 400-bp antisense cDNA construct of human PC cell derived growth factor inhibits PC cell derived growth factor protein expression and tumor growth in nude mice following subcutaneous injection in the breast area (see Examples 9-11, Table 3, and Figures 3,

4, and 15). The prior art teaches granulin/PC cell derived growth factor from many different species with many different sequences. For example the art teaches GenBank Accession Numbers BC010577; BC000324; NM_008175; BT026179; DQ369750; AF273480; AF273481; AF273479; DQ004683; NM_017113; and BT006844, for example. However, neither the instant specification, nor the prior art describe a method of inhibiting the growth of a tumor cell, or a method of inhibiting the expression of PC cell derived growth factor protein in a cell, comprising administering a PC cell derived growth factor antisense oligonucleotide to the tumor cell, wherein said antisense oligonucleotide inhibits the growth of the tumor cell or inhibits the expression of PC cell derived growth factor, other than the 400-bp antisense cDNA construct of human granulin/PC cell derived growth factor.

At the outset, it is noted that the rejected claims do not recite any sequence identifier relating to PC cell derived growth factor. This sequence is thus considered to be defined by its function (i.e. the activity of PC cell derived growth factor) rather than by any one specific structure. Accordingly the claims embrace antisense oligonucleotides that inhibit the expression of PC cell derived growth factor, or any such molecule with analogous PC cell derived growth factor activity, known or yet to be discovered, along with any isoform or allele present within this species, or any variant, polymorphic or otherwise, that is within reasonable similarity from these families of proteins that retain PC cell derived growth factor activity.

To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in

the art would recognize that the inventor possessed the claimed invention at the time of filing. Thus, an applicant complies with the written-description requirement by describing the invention, with all its claimed limitations, and by using such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical, structure/function correlation, methods of making the claimed product, and any combination thereof. The representative sample requirement may be satisfied by supplying structural or functional information, or a combination of both, such that one of skill in the art would be satisfied that applicants were in possession of the genus as claimed. Further, the size of the representative sample required is an inverse function of the unpredictability of the art.

See the January 5, 2001 (Vol. 66, No. 4, pages 1099-1111) Federal Register for the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement. These guidelines state: "[T]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including

description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention.

Further, See MPEP § 2163, which states "[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence."

In order to synthesize the antisense oligonucleotides that inhibit the expression of PC cell derived growth factor and to practice the methods claimed, one of skill would first need the sequence of the PC cell derived growth factor in order to synthesize said antisense oligonucleotides. However, one of skill in the art could not immediately envision the genus of antisense oligonucleotides that inhibit the expression of PC cell derived growth factor from the disclosure of the 400-bp antisense cDNA construct of granulin/PC cell derived growth factor, targeted to only the human sequence, particularly in the absence of any teaching by way of structure or reference to active domains or regions. The genus is not immediately envisioned because the genus of antisense oligonucleotides that inhibit the expression of PC cell derived growth factor is considered to include not only the 400-bp antisense cDNA construct of human granulin/PC cell derived growth factor of the instant invention, but also any such

molecule with analogous PC cell derived growth factor activity, known or yet to be discovered, along with any isoform or allele present within this species, or any variant, polymorphic or otherwise, that is within reasonable similarity from these families of proteins that retain PC cell derived growth factor activity. However, the distinguishing characteristics of the claimed genus are not considered to be described herein, or in the prior art. Thus, because one of skill in the art could not envision an antisense oligonucleotide that inhibits the expression of PC cell derived growth factor, other than the 400-bp antisense cDNA construct of human granulin/PC cell derived growth factor, one of skill would not be convinced that applicants were in possession of antisense oligonucleotides that inhibit the expression of PC cell derived growth factor sequences that are heretofore undescribed.

Claims 30, 33, and 36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is new matter rejection.**

Claims 30 and 33 recite the limitation, "wherein said oligonucleotide is at least about 15 nucleotides". This limitation appears to be new matter as the instant specification does not appear to have support for the term, "at least about 15 nucleotides". While the instant specification has support for the term, "at least 20" (see

original claim 17), support for at least 20 does not inherently or explicitly support the term, "at least about 15".

Claim 36 recites the limitation, "wherein the proliferation of the tumor cell is inhibited by at least about 80 percent". This limitation appears to be new matter as the instant specification does not appear to have support for the term, "at least about 80 percent". While the instant specification has support for the limitation, "wherein the proliferation of the tumor cell is inhibited by 80% (see pages 67 and 68, [00198] and [00200], respectively), support for 80% does not inherently or explicitly support the term, "at least about 80 percent".

Applicants are encouraged to point out where support for "at least about 15 nucleotides" and "at least about 80 percent" are found in the instant specification.

Applicant is required to cancel the new matter in the reply to this Office Action.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

tcg
August 14, 2006